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Direzione Scientifica

Milano, 14.10.52

Dear Bill,

Thank you for your letter and manuscript, and pardon me for answering so late. I have been busy on a variety of duties; by the way, I am enclosing some pictures taken at Pallanza which I have been sending around, including some that were not circularised. Meanwhile I had a letter from Joshua, who states: "I was delayed a few days in studying the 'final' version of our JGM paper. I must admit that it does read better now even than the American version. In order to avoid confusion I think that all corrections in proof should be cleared through you. If some changes are possible, I would like to discuss the following." The changes he suggests are unfortunately given on the basis of another manuscript, with different page numbers, but I think I can understand most of them, with a few exceptions which you may be able to clear, if you still have a copy of the manuscript which was sent to Lederberg. All references given here will refer to the manuscript in my hands; if necessary I may send it back to you, I am keeping it at present in view of having a few copies typed.

p.6, lines 19-22, ~~delete~~ delete sentence: "Aeration was carried out either by rolling the tubes (Milan) or by bubbling air through the medium (Madison)".

p.6 line 18, insert: " (by rolling)" after "aeration".

p.9, line 12. Instead of "enzyme inhibitors(...)", write:

"inhibitors of enzymes(...)"

p.10, lines 9-10. Instead of "perhaps more important", write: "may influence".

p.12, line 12. Here (at least I hope it is here: Joshua gives this as page 9 line 20 of his copy) Lederberg criticizes the use of transduce in the passive sense, as he himself has been doing in the past. Perhaps it might be better to say: F- strains can readily be ~~transformed~~ transformed by infection into F+, so that F+....

p.12 lines 23-21 (given as lines 21-29 page 9 of the L's manuscript). Lederberg believes this is too near the American version and should possibly be paraphrased. I doubt that I can do it properly. Have you any suggestions?

p.19 line 22. instead of "prototrophs" write "zygotes".

p.20 line 2. Delete "physical" before the word "basis". Alternatively, I may suggest to write "mechanism" instead of physical (basis).

p.27. Would it be possible to suggest the following rather drastic alteration, to eliminate some confusion and point out more

clearly what Lederberg thinks about it. At line 22, delete after "reduction", and delete also lines 23, 24 ~~and~~ lines 1, 2 of next page. Add instead: ~~xxxxxx data from the work xxx Heterozygotes (by Lederberg)~~ ~~may~~ the word "definite" before "evidence" at line 19 of page 27. In fact, Lederberg believes that elimination occurs after fertilisation, on the basis of data which I think might be explained on somatic crossing-over of Pontecorvo's type.

There are two further points in Lederberg's letter, which I cannot make out clearly. If, as I hope, you still have a copy of the manuscript which was sent to him, you may be able to understand them, otherwise I shall ask him to check them on the manuscript in my hands.

The first point says: "pl3 line 21. F+ is correct. It might be better to omit this paragraph (which is identical with one in the American version) or ^{insert the information} ~~xxxx~~ elsewhere." I do not know to what this refers: If ~~xxxxxx~~ you can find out, and think ~~xxxxxx~~ the paragraph can be omitted, so much the better.

The second point of Lederberg's letter says: "pl8 last PAR. The argument appears to be circular (as one defines F+ in terms of fertility) until one reaches the discussion of Hfr. If one can still make so drastic a change (and I very hesitantly suggest this) it might be better to reorganize the paragraph, beginning with the notion that Hfr forms an apparent exception to the rule that an F+ agent is essential. However, etc. to the distinction between the F agent and the F+ state." The last ~~xxxx~~ sentence seems incomplete, but I can probably understand at least approximately what it all means: I am asking Lederberg whether it might be enough, to eliminate circularity in the argument, to ~~alter~~ ^{delete} the sentence in brackets in line 18, p. 24; ~~to read~~ "(as shown by transduction to F-) "instead of" (i.e. of the F+ state)". In doing so I am assuming that what he gives as pl8 last PAR corresponds to what is, in my text, p. 24 last PAR. ~~xxxx asking Lederberg to check the first xxxxxx certain points quoted above, so that you may not need to worry about it, for the time being.~~

I have personally a few alterations to suggest. First, I have checked the number of ~~xxxx~~ so called strain W 927, page 22 line 16, and it is actually W 945. Second, for reasons that I shall explain with more detail later, I would now prefer to use the ~~xxxx~~ symbol ϕ for F when mentioning the agent or virus (keeping F for F state), which would imply correcting it in almost two dozens different lines. I have however to consult Lederberg on this point, and you may also have to say against it.

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Milano, 14.10. Continua

Third, a more careful analysis which I have done of my own data suggest that hypothesis 2 at the end of the paper ~~may~~ is untenable. This analysis was carried out in view of a letter I had from Watson, suggesting, incidentally, that you, he and I write a note about the possibility of interpreting the data on the basis of two chromosomes, one of which is not always, or rarely, included in the ~~F+~~ gamete. My data of the JGM paper do not corroborate, but do not exclude the hypothesis; in any case, they do not corroborate my hypothesis of a different ploidy of F+ and F- parents. I wonder whether one might either cancel it out, which would mean deleting the last paragraph of the paper, and alter in a few places the preceding paragraph ~~xxxx~~ putting forward only one hypothesis, or, if this is incompatible with the editor's policy, add a few words about the bad agreement between hypothesis two and the data of table 2. I am myself surprised at my laziness in not trying to test the hypothesis numerically before writing it on a paper. In fact, an analysis of the data reveals a ~~tendency~~ highly localised tendency to break in the region between Gal and Xyl (almost as if there were, in fact, two separate chromosomes, but not quite). What do you think about Jim's proposal of a joint note? Personally I have no paternity in the interpretation, which seems interesting, anyhow, and have little to add to it, so that I do not know whether I should join in.

A fourth minor note about the paper :p22 line 17, when the order of the markers is given, I should put Ara-TL-between brackets, and leave the minus sign out after TL, thus : S-Mal-Xyl-Gal-Lac-(Ara-TL) to indicate that the reciprocal position of Ara and TL is not clear ;also all the signs should not be minus signs, but only serve to separate the symbols(I hope it is clear what I mean by this last sentence).

I think it will not be necessary to send a copy of the proofs to Joshua, as he proposes that they be cleared through ~~me~~ (and you too, obviously).

I hope this will be all, and excuse me for this exceedingly boring letter. Your help in all the matter has been invaluable, and you must allow me to ask the Editor to add some lines of thanks for your help, in the revision of the manuscript.

Work has progressed in the last weeks, and while I was trying to ~~sixdown~~ proceed to the work of analysing maps, I was again caught by a side problem, as has ~~always~~ happened repeatedly in the past,

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and am spending most of the time with a new strain (it is actually an old one, which I never analysed properly) which is an F- with unusual characteristics. It crosses only to F+ but with a yield about 25 times smaller than usual. My interest in it was aroused by the fact that I could not transform it into F+ by infection. When testing the progeny between it and an F+ strain, I found half of the progeny was F+. I do not^{yet} know whether the F- recombinants are transducible to F+, which is of course an essential point, but it seems probable that we have here a strain mutated in a locus (?) which does not support the multiplication (and perhaps, even the adsorption) of the F virus. This would be further evidence against the idea of F as a carrier, though objections can be made against such evidence at this ~~pre~~ early point of the investigation. The fact suggested to me to use the symbol ϕ for the virus, rather than F, because situations like this have arisen repeatedly in the genetics of other organisms, and it has been customary to call the symbiotic virus with the greek letters, and the two alleles of the locus ~~xxxx~~ controlling the virus/ as F, f, (the ~~first~~ capital letter referring to the ~~xxxx~~ allele permitting growth of the virus, and the small letter to the allele inhibiting it). This is not very important, anyhow, and I cannot yet assert with confidence that the new facts can be seen in this light; in any case, I should like to know what you and Lederberg think about it. I shall let you know the further developments.

Thank you for sending the fly wheel toy motor, my children will be delighted with it. There is one further favor that I should like to ask you. I remember that in the earlier correspondence, you mentioned (I think to Lederberg) that a chap called Lightbown had found a streptomycinase. I should be interested in it (not for research, but for routine purpose, in view of using it for blood cultures). Could you perhaps let me have the information necessary to ~~xxx~~ know how the enzyme is made, and the strain producing it?

I have no idea yet whether it will be possible to me to come to England next year. However, I trust I shall see you again for the Genetics and Microbiology Congress. Dates will be 24-31 August and 6-12 Sept. respectively. Meanwhile there will be the Biometry Conference, where I have again some time to waste on organization, but you might like to spend the interval sightseeing. Lederberg should come also.

With best greetings also from Pupa for Nora and you. Pupa is working for her examination in Physiology and is in a very bad temper.

Yours sincerely

Luca